
Identification of HECT E3 ubiquitin ligase family genes involved in stem cell regulation and regeneration in planarians.

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Public Summary:

E3 ubiquitin ligases constitute a large family of enzymes that modify specific proteins by covalently attaching ubiquitin polypeptides, but the biological roles of most ubiquitin ligases remain poorly understood. We analyzed the function of one class of E3s (the HECT domain family of E3 ubiquitin ligases) in stem cell biology and tissue regeneration in planarians and determined that orthologs of *huwe1*, *wwp1*, and *trip12* had roles in tissue regeneration. Taken together, this work provides insight into the roles of HECT E3 ligases in tissue regeneration and demonstrate that planarians will be a useful model to evaluate the functions of E3 ligases in stem cell regulation.

Scientific Abstract:

E3 ubiquitin ligases constitute a large family of enzymes that modify specific proteins by covalently attaching ubiquitin polypeptides. This post-translational modification can serve to regulate protein function or longevity. In spite of their importance in cell physiology, the biological roles of most ubiquitin ligases remain poorly understood. Here, we analyzed the function of the HECT domain family of E3 ubiquitin ligases in stem cell biology and tissue regeneration in planarians. Using bioinformatic searches, we identified 17 HECT E3 genes that are expressed in the *Schmidtea mediterranea* genome. Whole-mount in situ hybridization experiments showed that HECT genes were expressed in diverse tissues and most were expressed in the stem cell population (neoblasts) or in their progeny. To investigate the function of all HECT E3 ligases, we inhibited their expression using RNA interference (RNAi) and determined that orthologs of *huwe1*, *wwp1*, and *trip12* had roles in tissue regeneration. We show that *huwe1* RNAi knockdown led to a significant expansion of the neoblast population and death by lysis. Further, our experiments showed that *wwp1* was necessary for both neoblast and intestinal tissue homeostasis as well as uncovered an unexpected role of *trip12* in posterior tissue specification. Taken together, our data provide insights into the roles of HECT E3 ligases in tissue regeneration and demonstrate that planarians will be a useful model to evaluate the functions of E3 ubiquitin ligases in stem cell regulation.

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